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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,288	06/08/2000	Guo-Liang Yu	PF343P3C5	1519

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,288	YU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-91,118-124,148-180 and 183-186* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-91, 118-124, 148-180, 183-186* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 02 December 2003 has been entered in full. Claims 85, 118, 148, 158, 166, and 174 are amended. Claims 183-186 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The declaration of Dr. David Hilbert filed under 37 CFR § 1.132 on 02 December 2003 has been received and considered.

Claims 85-91, 118-124, 148-180, and 183-186 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2 of the previous Office Action (03 June 2003) are *withdrawn in part* in view of the amended specification (03 December 2003). Please see section on Specification, below.

2. The rejections of claims 85-91, 118-124, and 148-180 under 35 U.S.C. 112, second paragraph, as set forth at pg 11-12 of the previous Office Action (03 June 2003) are *withdrawn* in view of the amended claims (03 December 2003).

Specification

3. Patent applications are referenced throughout the disclosure (for example pg 433, lines 12-14). The status of the applications must be updated. The basis for this objection is set forth at pg 2 of the previous Office Action (03 June 2003).

Applicant asserts that amendments to the specification address the objection. However, at pg 342, paragraph [0895], the status of case 09/005,874 still needs to be updated. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 85-91, 118-124, 148-180, and 183-186 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 2-11 of the previous Office Action of 03 June 2003 and at pg 2-6 of the Office Action of 13 August 2002.

The claims are directed to a method of treating an autoimmune system disease or disorder or rheumatoid arthritis comprising administering to an individual an effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of residues 134-285 of SEQ ID NO: 2. The claims also recite a method of inhibiting B lymphocyte proliferation, differentiation, or survival by administering various fragments of the amino acid of SEQ ID NO: 2. The claims recite a method of inhibiting B lymphocyte proliferation, differentiation, or survival comprising administering to an individual an effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of residues 134-285 of SEQ ID NO: 2. Finally, the claims are directed to a method of treating an autoimmune disease or disorder or rheumatoid arthritis comprising administering to an individual an effective amount of an antagonistic antibody that specifically binds an isolated neutrokine-α protein purified from a cell culture

wherein said cell culture comprise a polynucleotide encoding amino acids 1-285 of SEQ ID NO: 2.

The declaration under 37 CFR 1.132 filed 02 December 2003 is insufficient to overcome the rejection of claims 85-91, 118-124, 148-180, and 183-186 based upon the insufficiency of disclosure under 35 U.S.C. § 112, first paragraph, as set forth in the last Office action. Please see response to arguments, below.

Applicant's arguments (03 December 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that as of the earliest effective priority date of the present application, there have been art recognized standards for determining the optimal quantity, duration, and route of administration of an antibody. Applicant cites Box 5 from Waldmann (Nat Med 9:269-277, 2003) to emphasize that several monoclonal antibodies were already approved by the FDA for administration to humans or in late stage clinical trials at the time of the earliest effective priority date of the instant application.

Applicant's arguments have been fully considered but are not found to be persuasive. Such broad brush assertions that there are art recognized standards for determining the optimal quantity, duration, and route of administration of an antibody do not constitute adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirically to determine how to practice the suggested method to obtain the therapeutic results required by the claims. The specification does not disclose the optimal quantity, duration, and route of administration of an antagonistic anti-neutrokine-alpha antibody (see pages 180-201 of the specification; paragraphs [0052-0053]). There is also little guidance in the specification for

one skilled in the art to determine these optimal conditions. Such trial and error experimentation is considered undue. A large quantity of experimentation would still be required by one skilled in the art to determine the optimal quantity, duration, and route of administration of an anti-neutrokine-alpha antibody to treat all possible autoimmune diseases or disorders, rheumatoid arthritis, and inhibition of B cell proliferation, differentiation, or survival. Although Waldmann reviews the progress of the development of antibodies and lists the monoclonal antibodies approved by the FDA, there is no nexus between the antibodies listed in Box 5 and the anti-neutrokine-alpha antibody of the present invention. The antibodies in Box 5 of Waldmann each bind different target proteins, have different functions, and treat different conditions than the neutrokine-alpha protein of the instant application. Waldmann simply teaches that monoclonal antibodies are *emerging* as useful immunotherapeutics. In fact, Box 5 of Waldmann discloses that only 11 monoclonal antibodies have received FDA approval.

(ii) Applicant submits that according to the Federal Circuit, "a considerable amount of experimentation is permissible, if it is routine" *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Jackson*, 217 USPQ 804 (Board of Patent Appeals and Interferences, 1982)). Applicant reminds the Examiner that while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration (*In re Angstadt,* 190 USPQ 214 (C.C.P.A. 1976); *In re Vaeck*, 947 F. 2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). Applicant contends that because methods of determining the optimal quantity, duration, and route of administration of an antibody were known in the art, one skilled in the art could

determine, without undue experimentation, the optimal quantity, duration, and route of administration of an antagonistic anti-neutrokine-alpha antibody.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as indicated above, such broad brush assertions that there are art recognized standards for determining the optimal quantity, duration, and route of administration of an antibody do not constitute adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirically to determine how to practice the suggested method to obtain the therapeutic results required by the claims. The specification does not disclose the optimal quantity, duration, and route of administration of an antagonistic anti-neutrokine-alpha antibody (see pages 180-201 of the specification). There is also little guidance in the specification for one skilled in the art to determine these optimal conditions. Such trial and error experimentation is considered undue. A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein

one skilled in the art may not necessarily treat all possible autoimmune diseases or rheumatoid arthritis or inhibit B cell proliferation, differentiation, and survival by administration of an anti-neutrokine-alpha antibody.

(iii) Applicant asserts that the "problems" encountered in the development of therapeutic antibodies relied upon by the Examiner to support the rejection (Ballow et al.; JAMA 278: 2008-2017, 1997; Moore, Clin Chem 35: 1849-1853, 1989) are related to either the safety or efficacy of the antibody or to the production of quantities sufficient for commercial scale manufacturing. Applicant argues that such concerns are not appropriate considerations for patentability but rather, are the concerns of the FDA. Applicant indicates that the problems of administration of non-human antibodies to human subjects which may induce an anti-foreign antibody immune response has not prevented the FDA from approving non-human or chimeric antibodies for use in human patients.

Applicant's arguments have been fully considered but are not found to be persuasive. The references were cited by the Examiner in the previous Office Action to indicate the state of the art at the time the application was filed. A few of the issues raised in these references include difficulty in making physical contact between the antibody and the target antigen and nonoptimal systemic half-life of antibodies (among others). These concerns are appropriately raised under the 35 U.S.C. § 112, first paragraph for enablement because one skilled in the art would not be able to predict the activity or effect of the neutrokine-alpha antibody once administered to a subject, especially treatment of autoimmune diseases or rheumatoid arthritis. For example, if the anti-neutrokine-alpha antibody has problems contacting the protein or has a nonoptimal systemic

half-life, how many times must the skilled artisan administer the antibody to treat all possible autoimmune diseases or rheumatoid arthritis, as recited in the claims? For how long? At what dosage? Again, the specification of the instant application does not provide any guidance for the skilled artisan to determine such conditions. Therefore, a large quantity of experimentation may be required by one skilled in the art to overcome some of the issues raised by Moore and Ballow et al. in order to treat all possible autoimmune diseases or rheumatoid arthritis with an anti-neutrokine-alpha antibody. Such experimentation is considered undue.

(iv) Applicant argues that the specification teaches that neutrokine-alpha antagonists can be used to treat autoimmune diseases (paragraphs [0050] and [0620]), thereby informing one of skill in the art that either excess neutrokine-alpha protein levels and/or excessive neutrokine-alpha activity would be present in autoimmune diseases. Applicant submits that post-filing date data confirms that increased levels of neutrokine-alpha correlate with murine models of autoimmunity (Gross, Nature 404: 995-999, 2000). Applicant states that increased levels of neutrokine-alpha have been observed in patients with rheumatoid arthritis and systemic lupus erythematosus (Cheema et al, Arthritis Rheum 44: 1313-1319, 2001; Zhang et al. J Immunol 166: 6-10, 2001). Applicant also contends that the Hilbert declaration indicates that the data were used to support HGS' IND application that enabled HGS to begin human clinical trials for use of the anti-neutrokine-alpha antibody (Lymphostat B) in the treatment of systemic lupus erythematosus.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges the post-filing date references indicate that increased levels of neutrokine-alpha correlate with a murine model of systemic lupus erythematosus and that

increased levels of neutrokine-alpha are found in patients with rheumatoid arthritis and systemic lupus erythematosus. However, these references do not disclose the administration of an anti-neutrokine-alpha antibody for treatment of these conditions or any other autoimmune diseases or disorders, only that it would be desirable to do so. Together, the specification of the instant application and the post-filing date references do not provide adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirically to determine how to practice the suggested method to obtain the therapeutic results required by the claims. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed".

The Examiner is unable to appropriately comment on Applicant's statement that HGS has a successful IND Application for the initiation of human clinical trials for the use of an anti-neutrokine-alpha antibody for the treatment of systemic lupus erythematosus because it is not clear what specific evidence has been presented to the FDA. Furthermore, the Examiner is unable to determine if there is support in the specification of the instant application for the evidence that may have been submitted.

It is noted that Dr. Hilbert is employed at HGS, the assignee of the instant patent application, and is therefore an interested party.

(v) Applicant asserts that the specification teaches antagonistic anti-neutrokine-alpha antibodies that inhibit the stimulatory effect that neutrokine-alpha has on lymphocytes would be useful in the treatment in the genus of autoimmune diseases, which by definition are diseases that

occur when autoreactive B and/or T lymphocytes are stimulated. Applicant argues that in the Declaration, Dr. Hilbert confirms that autoimmune diseases result from the activity of autoreactive B cells and T cells and that the pathologies observed in autoimmune diseases result from damage inflicted by autoreactive cytotoxic T cells and/or autoantibodies secreted by autoreactive B cells. Applicant states Dr. Hilbert indicates that even though different autoimmune diseases may have different pathologies, every autoimmune disease involves a common mechanism, i.e., autoreactive B and/or T cell activity. Applicant contends that the declaration of Dr. Hilbert indicates that autoimmune diseases are treated with immunosuppressive therapies that inhibit activated lymphocytes, irrespective of their location in the body (paragraph 5; Table 24-1 of Ballow et al.). Applicant states that the Hilbert declaration explains anti-neutrokine-alpha therapy will act as a lymphocyte immunosuppressant by blocking neutrokine-alpha's ability to act as a costimulatory signal necessary for lymphocyte activation.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action, increased B cell activity is not the only characteristic of autoimmune diseases and neutrokine-alpha is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases. Although autoimmune diseases result from the activity of autoreactive B cells and T cells, one skilled in the art would not be able to predict that an anti-neutrokine-alpha antibody would be able to treat all possible autoimmune diseases because each disease has other steps/mechanisms involved in its manifestation. The current state of the art is such that there has been no single agent identified that could treat all possible autoimmune diseases. Furthermore, there are no methods or working examples in the instant specification or the post-filing date references

supplied by the Applicant to indicate that anti-neutrokine-alpha antibodies are able to treat all autoimmune diseases, (including rheumatoid arthritis) or the inhibit B lymphocyte proliferation, differentiation, or survival. A large quantity of experimentation would be required of the skilled artisan to determine the optimal quantity, duration, and route of administration of an anti-neutrokine-alpha antibody for all possible autoimmune diseases, as well as to successful treat these diseases. Such experimentation is considered undue.

It is noted again that again that Dr. Hilbert is employed at HGS, the assignee of the instant patent application, and is therefore an interested party.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to inhibit the proliferation, differentiation, and survival of B lymphocytes in an individual by administration of anti-neutrokine-alpha antibody and to treat all possible autoimmune diseases and disorders, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of an anti-neutrokine-alpha antibody in the body, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
27 May 2004

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